R E M A R K S

New claim 56 combines features of claims 40, 29 and 26.

New claim 57 recites the features of claim 45.

New claims 58 to 60 were added in view of page 9,lines 5 to 7 of the Office Action.

With respect to Item No. 4 at the bottom of page 3 of the Office Action, the Examiner's attention is directed to applicants' REQUEST FOR INITIALED COPIES OF FORMS PTO/SB/08A AND PTO/SB/08B filed June 5, 2003, wherein copies of the references requested by the Examiner were provided.

In reply to Item No. 8 at the bottom of page 4 of the Office Action, a new title is furnished hereinabove.

In response to Item No. 9 bridging pages 4 and 5 of the Office Action a new Abstract of the Disclosure is submitted concomitantly herewith.

Claims 40 to 43 and 45 were objected to for the reasons set forth on page 5 of the Office Action.

Claim 40 was amended to avoid these objections.

Claims 40, 42, 43 and 45 were rejected under 35 USC 112, second paragraph, for the reasons set forth in Item Nos. 12 and 13 on pages 5 and 6 of the Office Action.

Claim 40 was amended by following the Examiner's suggestions.

Claims 40 to 43 and 45 were rejected under 35 USC 112, second paragraph for the reasons indicated in Item No. 14 at the bottom of page 6 of the Office Action.

Claim 40 was amended by inclusion of features from claim 1.

The wording of new claims 56 and 58, with respect to the vector, was made in view of the Examiner's comments in Item No. 14 of the Office Action and was discussed with the Examiner during a telephone interview between the Examiner and the undersigned on September 2, 2003.

Claim 42 was rejected under 35 USC 112, second paragraph for the reasons indicated in Item No. 15 at the top of page 7 of the Office Action.

Claim 42 was amended to avoid the 35 USC 112, second paragraph rejection.

Claim 43 was rejected under 35 USC 112, second paragraph for the reasons indicated in Item No. 16 at the middle of page 7 of the Office Action.

The above amendment to claim 43, which was discussed with the Examiner during the aforesaid September 2, 2003 telephone

interview, is considered to avoid the 35 USC 112, second paragraph rejection.

Claims 40, 42, 43 and 45 were rejected under 35 USC 112, first paragraph for the reasons indicated in Item No. 17 on pages 7 to 9 of the Office Action.

Claim 40 was amended by inclusion of a feature of original claim 36 (also see page 8, lines 17 to 20 of the specification). Claim 40 was also amended to recite that the variant is capable of "increasing the transcription of a gene selected from the group consisting of mlcA, mlcB, mlcC and mlcD", which is consistent with the Examiner's statement in the last full sentence on page 8 of the Office Action.

Claims 40 to 43 and 45 were rejected under 35 USC 112, first paragraph for the reasons indicated in Item No. 18 on pages 9 to 10 of the Office Action.

In reply to this 35 USC 112, first paragraph rejection, a DECLARATION OF MICROORGANISM DEPOSIT of Mr. Takashi SHODA dated July 7, 2003 for *Escherichia coli* pSAKexpR SANK 72599 (FERM BP-7006) is submitted concomitantly herewith.

Withdrawal of the above 35 USC 112, first paragraph rejection is therefore respectfully requested.

Claims 40 to 43 and 45 were rejected under 35 USC 112, first paragraph for the reasons indicated in Item No. 19 on pages 10 to 11 of the Office Action, wherein the position was taken that the specification was enabled for methods using only host cells that contain the biosynthetic pathway for ML-236 (for example, *P. citrinum*).

In reply to this 35 USC 112, first paragraph rejection, submitted concomitantly herewith is a DECLARATION UNDER 37 CFR 1.132 of Yuki ABE dated October 6, 2003. It is respectfully submitted that the enclosed DECLARATION UNDER 37 CFR 1.132 of Yuki ABE provides a showing for several microorganisms and thus serves to demonstrate enablement for the full scope of the presently claimed invention.

It is therefore respectfully submitted that the present claims and specification comply with all the requirements of 35 USC 112.

Claims 40, 42, 43 and 45 were rejected under 35 USC 102 as being anticipated by WO 01/12814 for the reasons set forth in Item No. 20 at the top of page 12 of the Office Action.

An English-language translation of WO 01/12814 is enclosed.

WO 01/12814 teaches a genomic DNA fragment having 34203 base pairs. In said genomic DNA fragment, there is a structural gene termed mlcR. The genomic mlcR is transcribed into the pre-mRNA.

In general, any introns that existed in a pre-mRNA are removed by splicing and then the mature mRNA without introns is produced. In general, however, the length and positoin/location of introns that existed in the pre-mRNA cannot be determined directly and primarily only from the corresponding genomic gene sequence. Accordingly, the nucleotide sequence of the corresponding cDNA and the deduced amino acid sequence cannot be determined directly and primarily only from the corresponding genomic gene sequence.

The inventors of the present application cloned the cDNA corresponding to the mature mRNA of mlcR and determined the nucleotide sequence (SEQ ID NO 41). Only after comparing applicants' SEQ ID NO 41 with the genomic gene mlcR, two introns were shown to exist in the pre-mRNA of mlcR/the genomic genemlcR.

The inventors are convinced that applicants' nucleotide sequence of mlcR cDNA could not be determined by one of ordinary skill in the art based on the nucleotide sequence of 34203-bp genomic DNA fragment disclosed in WO 01/12814 or any other teachings of WO 01/12814, such as the transcriptional initiation

site (Table 5), the translational initiation codon (Table 5) and the translational termination codon (Table 8).

In reply to the position taken in the Office Action that WO 01/12814 contains a variant of SEQ ID NO 42, applicants respond as follows:

As discussed above, the 34203-bp genomic DNA fragment of WO 01/12814 contains a genomic gene termed mlcR, which can be transcribed into the pre-mRNA. Prior to the present invention, one of ordinary skill in the art would not have known that two introns would need to be removed from the pre-mRNA by splicing to obtain the mature mRNA. The cDNA, which is completely complementary to said mature mRNA, encodes applicants' SEQ ID NO 42. The nucleotide sequence of the cDNA (the mlcR cDNA) is shown as applicants' SEQ ID NO 41.

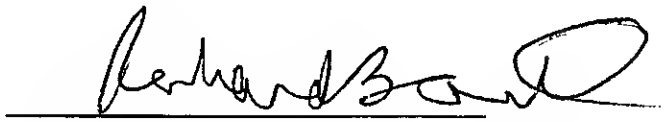
In view of the above, withdrawal of the 35 USC 102 rejection is respectfully requested.

Reconsideration is requested. Allowance is solicited.

Enclosed is a check for $176 in payment of five total extra claims and one additional independent claim.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Encs.: (1) PETITION FOR EXTENSION OF TIME
(2) DECLARATION OF MICROORGANISM DEPOSIT dated July 1, 2003
(3) DECLARATION UNDER 37 CFR 1.132 of Yuki ABE dated October 6, 2003
(4) ENGLISH-LANGUAGE TRANSLATION OF WO 01/12814
(5) CHECK FOR $176

ABSTRACT OF THE DISCLOSURE

Polynucleotides, such as DNA, are provided which accelerate the biosynthesis of a HMG-CoA reductase inhibitor, ML-236B, in an ML-236B producing micro-organism when introduced in the ML-236B producing micro-organism. Pravastatin, which is an HM-CoA reductase inhibitor, can be obtained using *Streptomyces carbophilus* by microbial conversion of ML-236B produced by *Pencillium citrinum*. The polynucleotides encode a gene (such as mlcA (polyketide synthase), mlcB (polyketide synthase), mlcE (efflux pump) or mlcR (transcription factor). Provided are vectors into which such polynucleotides are incorporated; host cells transformed by such vectors; and proteins expressed by such vectors. A method for producing ML-236B using such polynucleotides and/or proteins which comprises recovering ML-236B from a culture of the host cell.